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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,291	12/04/2003	Stephen F. Badylak	3220-73986	7088

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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
10/09/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

indocket@btlaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/728,291	BADYLAK ET AL.	
	Examiner	Art Unit	
	ALLISON M. FORD	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-24* is/are pending in the application.

4a) Of the above claim(s) *17-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20090612*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response of 6/12/2009 has been received and entered into the application file. Claim 9 has been amended; no claims have been added or cancelled. Claims 9-24 remain pending in the current application, of which claims 17-24 remain withdrawn from consideration pursuant to 37 CFR 1.142(b), as being directed to a non-elected invention. Claims 9-17 have been considered on the merits.

Information Disclosure Statement

The information disclosure statement provided 6/12/2009 has been received and the references cited therein have been fully considered. The two references "lined-through" on the IDS were previously made of record on the PTO-892 (9/20/2007). An initialed copy of the IDS is being provided with this office action.

Response to Arguments

Applicants' arguments of 6/12/2009 have been fully considered. Each argument will be addressed below as appropriate. Rejections/objections not repeated herein have been withdrawn from consideration.

With regards to the rejection of claims 9-16 under 35 USC 112, second, as being indefinite, the amendment to claim 9 has obviated the rejection of record.

With regards to the rejection of claims 9-16 as being obvious under 35 USC 103(a), Applicants have traversed on the grounds that the claims, as amended, now specify that the graft composition is prepared by providing liver basement membrane substantially free of cells and seeding the hepatocytes on the liver basement membrane [which is] substantially free of cells. Applicants assert the claim language

now differentiates from the teachings of Naughton et al, as Naughton et al only disclose hepatocytes retain their functionality when seeded onto a *pre-established* stromal cell layer.

Applicants have further pro-offered that the instant invention yields unexpected results, specifically that that the current method provides the unexpected result of being capable of maintaining functional hepatocytes in culture, whereas the prior art only suggested the liver basement membrane composition could support and stimulate hepatocyte proliferation. Applicants stress that hepatocyte proliferation does not necessarily equate to maintenance of hepato-cellular function, whereas the hepato-cellular functions, as recited in the claims, are selected from the group consisting of albumin production, urea production, and cytochrome P450 activity. Applicants assert the maintenance of hepato-cellular functionality in *in vitro* cultures was not routine prior to the current invention, and assert their liver basement membrane supported superior functionality as compared to collagen-adsorbed collagen.

Applicants' argument regarding the difference between the instant invention and the method of Naughton et al is well taken. The amendment to claim 9 to require the hepatocytes to be seeded onto liver basement membrane [which is] substantially free of cells does differentiate from the teachings of Naughton et al.

However, a new ground of rejection is set forth over the teachings of Saad et al (In Vitro Cell Dev Biol, 1993).

Applicants' argument regarding unexpected results is not found persuasive in view of the teachings of Saad et al. Applicants have asserted that one of ordinary skill in the art would not have had a reasonable expectation that culturing hepatocytes on the liver basement membrane, as suggested by each of the Badylak references, would yield hepatocytes capable of maintaining functionality in vitro; however, Saad et al report that hepatocytes cultured on crude liver membrane fraction do retain their ability to secrete albumin and P450 (liver specific functions, i.e. functionality) (See Saad et al, Pg. 34, col.

2). Therefore, because Saad et al shows liver membrane fractions support retention of liver specific functions in hepatocytes cultured thereupon, and because the liver basement membrane of Badylak is derived from the same tissue source and necessarily has the same mix of natural proteins and extracellular matrix signaling molecules as the crude membrane fraction of Saad et al, one would have had a reasonable expectation that the liver basement membrane of Badylak would similarly support retention of liver specific cell functions. Therefore the claims remain rejected.

With regards to the non-statutory double patenting rejection of claims 9-16 over claims U.S. Patent No. 6,793,939, and of claims 1, 3, 12 and 14 of U.S. Patent No. 7,482,025, each in view of Badylak (WO 98/25637) and Naughton et al (US Patent 5,510,254), Applicants have reiterated their arguments presented against the rejection under the statute of 35 USC 103(a).

In response, for the same reasons as discussed above, the rejections are withdrawn, however new grounds of rejection are made based on the teachings of Saad et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9-16 are rejected under 35 U.S.C. 103(a) as being obvious over each of Badylak WO 98/25637 and Badylak US Patent 6,793,939 (national stage entry of PCT/US97/22727), each in view of Saad et al (In Vitro Cell Dev Biol, 1993).

It is noted the applied **patent** reference (US 6,793,939) has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes

prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2). Please note the WIPO publication is prior art under 35 USC 102(b) and cannot be overcome in such a manner.

In each reference Badylak disclose methods of inducing endogenous tissue formation at a site in need thereof by administering a graft composition comprising liver basement membrane in an amount effective to induce the repair of the tissue at the site of administration. Badylak disclose the graft composition can be administered as a multi-layered composition formed from two or more layers of liver basement membrane (See WO 98/25637 Pgs 8-9/ See USP '939 col. 6, ln 13-64). The thickness of individual layers/sheets would be routinely optimized to suit the intended implantation site's needs (size and shape). Badylak further state the basement membrane can be provided in various forms, including a fluidized liquid (which can also be considered a gel) or powder form (See WO 98/25637 Pg. 4-5/ See USP '939 col. 3, ln 45-col. 4, ln 11).

Badylak further disclose eukaryotic cells may be seeded onto the liver basement membrane prior to implantation to enhance the tissue replacement capabilities of the graft material upon administration. Cells corresponding to the target tissue site (target tissue site being the site to which the graft is being

administered to induce endogenous tissue formation) may be cultured on the liver basement membrane material, and the graft then implanted to the corresponding target tissue site. For example, Badylak discloses culturing keratinocytes on liver basement membrane for use as a skin graft, or culturing endothelial cells on liver basement membrane for use as a vascular graft. Badylak further discloses other cell types, including hepatocytes, may be cultured on the liver basement membrane (See WO 98/25637 Pg 12/ See USP '939 col. 8, ln 30-col. 9, ln 23).

It is understood that hepatocytes can quickly loss their functionality during *in vitro* culture; however Saad et al disclose that hepatocytes cultured on crude membrane fractions obtained from the liver support hepatocyte growth while retaining liver specific activities, including production of cytochrome P450 and production of albumin (See Saad et al, Pg. 34, col. 2). Saad et al suggest the natural mix of membrane proteins and extracellular signaling molecules available in the crude membrane fraction are responsible for supporting the liver specific functions of the hepatocytes (See Saad et al, Pg. 37, col. 2). Because Saad et al teach crude membrane fractions from the liver are capable of maintaining liver specific activity of hepatocytes cultured thereupon, it is submitted that one of ordinary skill in the art would have had reasonable expectation that the liver basement membrane, used by Badylak et al, would have similar capabilities, based on the fact that the crude membrane fraction of Saad et al and the liver basement membrane of Badylak are both acellular fractions of liver tissue which contain the proteins and extracellular signaling molecules present within the liver tissue in their natural state.

Badylak differs from the instant method in that, while he suggests producing a graft material comprising liver basement membrane with hepatocytes cultured thereupon, he does not disclose administering such a graft for use as a liver tissue graft to repair damaged or diseased liver tissue. Badylak further differs in that he does not report on the functionality of the hepatocytes once cultured on the liver basement membrane.

However, at the time the invention was made the need for a method of repairing damaged or diseased liver tissue was well recognized, and thus the artisan of ordinary skill would have been motivated to adapt the method of Badylak to include administering a hepatocyte-containing liver basement membrane graft material to a patient in need thereof in order to solve the recognized need in the art. One would have had a reasonable expectation of successfully implanting the graft material suggested by Badylak for the repair of damaged or diseased liver tissue because Badylak teaches tissues produced with the liver basement membrane can be implanted to repair damaged or diseased tissues in vitro by selecting the appropriate endogenous cell type for production of the graft. Furthermore, the teachings of Saad et al would have lead one to believe the liver basement membrane would have successfully supported hepatocyte growth in a manner such that the hepatocytes are at least *capable of* maintaining their functionality *in vitro*, and thus have had an effect upon administration *in vivo*. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 9-16 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,793,939, in view of Badylak (WO 98/25637), and further in view of Saad et al (In Vitro Cell Dev Biol, 1993).

The patented claims disclose methods of inducing the formation of endogenous tissue at a site in need thereof by implanting a graft composition comprising the same liver basement membrane as disclosed in the current claims; the patented claims differ in that they do not specify the liver as the endogenous tissue in need of repair, and they do not disclose hepatocytes being present on the liver basement membrane.

However, Badylak (WO 98/25637), which discloses the same liver basement membrane material for implantation to repair damaged tissue, disclose eukaryotic cells may be seeded onto the liver basement membrane prior to implantation to enhance the tissue replacement capabilities of the graft material upon administration. Badylak discloses hepatocytes amongst the cells that may be cultured on the liver basement membrane (See WO 98/25637 Pg 12). Saad et al report that hepatocytes cultured on crude liver membrane fractions retain their liver specific functions, including ability to produce albumin and cytochrome P450 (See Saad et al, Pg. 34, col. 2).

Therefore, though the current claims and the patented claims are not identical, they are not considered patentably distinct, because it would have been obvious to one of ordinary skill in the art to improve upon the patented method by including tissue-specific cells on the liver basement membrane material, as suggested by Badylak. The effect of the liver basement membrane on the hepatocytes, specifically supporting retention of liver specific activity of the cells would have been expected in view of the teachings of Saad et al.

Claims 9 and 12 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 12 and 14 of U.S. Patent No. 7,482,025, in view of Badylak (WO 98/25637), and further in view of Saad et al (In Vitro Cell Dev Biol, 1993).

The patented claims disclose methods of inducing the formation of endogenous tissue at a site in need thereof by implanting a graft composition comprising the same gelled liver basement membrane as disclosed in the current claims, and with endogenous cells cultured thereupon; the patented claims differ in that they do not specify the liver as the endogenous tissue in need of repair, and they do not disclose hepatocytes as the specific cell type cultured thereupon.

However, Badylak (WO 98/25637), which discloses the same liver basement membrane material for implantation to repair damaged tissue, disclose eukaryotic cells may be seeded onto the liver basement membrane prior to implantation to enhance the tissue replacement capabilities of the graft material upon administration. Badylak discloses hepatocytes amongst the cells that may be cultured on the liver basement membrane (See WO 98/25637 Pg 12). Saad et al report that hepatocytes cultured on crude liver membrane fractions retain their liver specific functions, including ability to produce albumin and cytochrome P450 (See Saad et al, Pg. 34, col. 2).

Therefore, though the current claims and the patented claims are not identical, they are not considered patentably distinct, because it would have been obvious to one of ordinary skill in the art to improve upon the patented method by including tissue-specific cells on the liver basement membrane material, as suggested by Badylak. The effect of the liver basement membrane on the hepatocytes, specifically supporting retention of liver specific activity of the cells would have been expected in view of the teachings of Saad et al.

Conclusion

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 6/12/2009 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Primary Examiner, Art Unit 1651